REMARKS

Claims 4 and 5 are pending in the application. No new matter has been introduced.

Rejection Under 35 U.S.C. §103(a), Over Neiss '733 (EP 0297733) In View of Deac, (Igiena, 19(3):167-73, 1970), as evidenced by Gibson, (Journal of Antimicrobial chemotherapy, 538-570, 1980)

Claims 4-5 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Neiss '733 in view of Deac, as evidenced by Gibson. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

Neiss '733

Neiss '733 discloses pharmaceutical compositions comprising catecholic butane. In particular, Neiss '733 shows data for nordihydroguaiaretic acid (NDGA) for the treatment of a variety of tumors or tumorous cells lines (Example 2, anti-carcinoma effects of NDGA; Example 3, anti-breast adenocarcinoma effects of NDGA; Example 4, anti-MC-1 sarcoid-derived cell line effects of NDGA; Example 5, anti-lung tumor effects of NDGA; Example 6, *in vivo* antitumor effects of NDGA; Example 7, antineoplastic activity of NDGA; Example 8, anti-tumor effects of NDGA; and Example 9, ability of NDGA to absorb sunlight).

Neiss '733 further discloses that its genus of catecholic butane can be used to treat acne in three passages as follows:

> (57) The invention relates to pharmaceutical compositions useful in the treatment of benign, premalignant and malignant solid tumours, especially those of the skin, and in the treatment of other disorders of the skin e.g. psoriasis and acne. The compositions comprise at least one catecholic butane. The preferred catecholic butane is nordihydroguaiaretic acid. The compositions are preferably applied topically or by intratumor or subcutaneous injection. The invention also includes sunscreening agents comprising at least one catecholic butane.

Abstract

> The methods according to the invention are also useful in the treatment of diseases and disorders of the skin such as acne and psoriasis, in aiding the healing of skin wounds and breaks in the skin and for antiviral, antibacterial and antifungal uses.

Page 2, lines 7-9.

> The pharmaceutical compositions of the present invention are also useful for the prevention of the occurance of and/or the treatment of disorders of the skin such as actinic keratosis, acne, psoriasis, skin wounds, warts, bacterial infections, fungal infections and viral infections.

Page 4, lines 20-22.

These three passages are all that Neiss '733 has to offer on this subject of acne treatment.

Deac

Deac discloses bactericidal effect of *Staphylococcus aureus in vitro.*

Gibson

Gibson discloses types of bacteria that may colonize pilosebaceous follicles.

The Examiner has failed to establish *prima facie* obviousness of the presently claimed invention

The Examiner is reminded of the standards to establish *prima facie* obviousness of the presently claimed invention over the cited references.

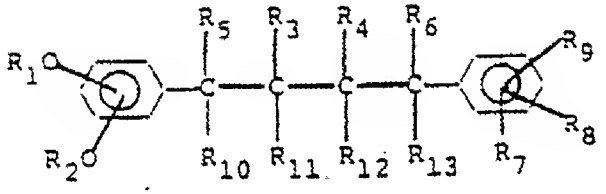
> The patentability of a claim to a specific compound or subgenus embraced by a prior art genus should be analyzed no differently than any other claim for purposes of 35 U.S.C. 103. " . . . The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) (Federal Circuit has "decline[d] to extract from *Merck* [*& Co. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989)] the rule that... regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it."). See also *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995). MPEP 2144.08.

MPEP 2144.08 further states:

> Consider the size of the prior art genus, bearing in mind that size alone cannot support an obviousness rejection. See, e.g., *Baird*, 16 F.3d at 383, 29 USPQ2d at 1552 (observing that "it is not the mere number of compounds in this limited class which is significant here but, rather, the total circumstances involved"). There is no absolute correlation between the size of the prior art genus and a conclusion of obviousness. *Id.* Thus, the mere fact that a prior art genus contains a small number of members does not create a *per se* rule of obviousness. However, a genus may be so small that, when considered in light of the totality of the circumstances, it would anticipate the claimed species or subgenus. For example, it has been held that a prior art genus containing only 20 compounds and a limited number of variations in the generic chemical formula inherently anticipated a claimed species within the genus because "one skilled in [the] art would... envisage *each member*" of the genus. *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962) (emphasis in original). More specifically, the court in *Petering* stated:
>
> A simple calculation will show that, excluding isomerism within certain of the R groups, the limited class we find in Karrer contains only 20 compounds. However, we wish to point out that it is not the mere number of compounds in this limited class which is significant here but, rather, the total circumstances involved, including such factors as the

limited number of variations for R, only two alternatives for Y and Z, no alternatives for the other ring positions, and a large unchanging parent structural nucleus. With these circumstances in mind, it is our opinion that Karrer has described to those with ordinary skill in this art each of the various permutations here involved as fully as if he had drawn each structural formula or had written each name.
Id. (emphasis in original). *Accord In re Schaumann*, 572 F.2d 312, 316, 197 USPQ 5, 9 (CCPA 1978) (prior art genus encompassing claimed species which disclosed preference for lower alkyl secondary amines and properties possessed by the claimed compound constituted description of claimed compound for purposes of 35 U.S.C. 102(b)). *C.f., In re Ruschig*, 343 F.2d 965, 974, 145 USPQ 274, 282 (CCPA 1965) (Rejection of claimed compound in light of prior art genus based on *Petering* is not appropriate where the prior art does not disclose a small recognizable class of compounds with common properties.). MPEP 2144.08

The Examiner refers to a catecholic butane of formula (II) as shown below:



(II)

wherein R_1 and R_2 are independently H, lower alkyl, lower acyl, or alkylene;
R_3, R_4, R_5, R_6, R_{10}, R_{11}, R_{12}, and R_{13} are independently H or lower alkyl;
R_7, R_8 and R_9 are independently H, hydroxy, lower alkoxy, lower acyloxy, or any two adjacent groups together may be alkylene dioxy.

The Examiner states that the catecholic butane of formula (II) in which R_1, R_3 and R_4 are CH_3; R_2, R_5, R_6, R_9, R_{10}, R_{11}, R_{12} and R_{13} are all hydrogen; and R_7 and R_8 together form a alkylene (methylene) dioxy group, is a diastereoisomer of the instantly claimed macelignan (erythro {(4-hydroxy,-3-methoxyphenyl)-4-(3,4, methlenedioxyphenyl)-2,3-dimethyl butane}).

The Examiner appears to assert that the presently claimed invention is obvious over the cited references merely because the presently claimed compound falls within the broad genus of formula (II) above. Applicants disagree with this approach taken by the Examiner. The Examiner must consider several factors in determining whether one of ordinary skill in the art would have been motivated to select the presently claimed macelignan from the broad catecholic butane genus that is disclosed in the Neiss '733 reference. The Examiner is again referred to MPEP 2144.08. In particular, the Examiner has failed to establish obviousness for at least the following three reasons.

The Neiss '733 genus is too large to obviate a compound that falls within the genus

First, the number of variable compounds that the Neiss '733 reference encompasses is at least in the thousands. Selecting one useful compound from the at least thousands of possibilities cannot on its face be obvious. Therefore, the presently claimed invention is not obvious over the cited references.

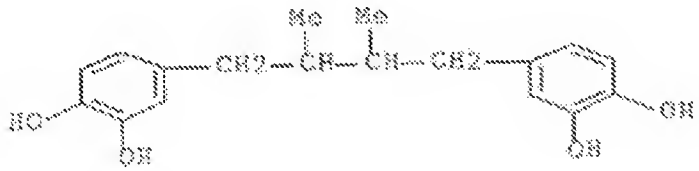
Neiss '733 points away from using macelignan within the genus of catecholic butanes

Second, even within Neiss '733, Neiss '733 internally does not point to the desirability of using the presently claimed macelignan compound. Therefore, a person of skill in the art at the time of the invention would be dissuaded from using macelignan in favor of compounds that are more similar to NDGA.

At page 5, lines 22-29, Neiss '733 discloses some desirable catecholic butanes as below:

> Examples of catecholic butanes include the d-, 1-, racemic mixture of d- and 1-, and meso-isomers of 1,4-bis(3,4-dihydroxyphenyl)-2,3-dimethylbutane; 1,4-bis (3,4- dihydroxyphenyl)butane; 1,4-bis (3,4-dimethoxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-diethoxyphenyl)-2,3-dimethyl-butane; 1,4-bis(3,4-dipropoxyphenyl)-2,3-dimethylbutane; 1-(3,4-dihydroxyphenyl)-4-(3′, 4′, 5′ -trihydroxyphenyl) butane; 1,4-bis(3,4-diacetoxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dipropionyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dibutyroyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-divaleroyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dipivaloyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dineopentylcarboxylphenyl)-2,3-dimethylbutane; 1-(3,4-dihydroxyphenyl)-4-phenylbutane and 1-(3,4-dihydroxyphenyl-4-(2,5 dihydroxyphenyl) butane. Mixtures of the Formula (II) catecholic butanes may be used in the instant compositions.

However, none of these "example" compounds, which are presumably desirable compounds for use in Neiss '733, describes a di-oxy cyclic structure attached to a phenyl group as in macelignan of the claimed invention. Instead, the Neiss '733 disclosure is more specifically focused on the activities of compound NDGA, which has the following formula,



which does not have a di-oxy cyclic structure as in the claimed macelignan. NDGA is the sole exemplified compound for use in various anti-tumor assays in Neiss '733. Therefore, although Neiss '733 mentions macelignan having di-oxy cyclic phenyl group as a member of its genus, in essence points away from the presently claimed compound because the focus of the Neiss '733 reference is entirely on NDGA and compounds similar to it.

In further support of the Neiss '733 reference pointing away from using macelignan, the Examiner's attention is directed to page 10, lines 16-22:

> The following compounds were prepared by a similar procedure:
> a) 1-(3,4-Dihydroxyphenyl)-4-(3,4,5-trihydroxyphenyl)butane;
> b) 1-(3,4-Dihydroxyphenyl)-4-phenylbutane
> c) 1-(3,4-Dihydroxyphenyl-4-(2,5-dihydroxyphenyl) butane;
> d) 1,4-Di(3,4-dihydroxyphenyl)-1,2,3,4-tetramethylbutane
> e) 1,4-Di(3,4-dihydroxyphenyl)-2-methyl-3-ethylbutane
> f) 1,4-Di(3,4-dihydroxyphenyl)-1-propyl-2-methyl-3-ethylbutane.

None of these cited compounds possesses a di-oxy cyclic phenyl group as in the presently claimed macelignan. Therefore, the Neiss '733 reference again internally points away from the claimed invention. Applicants also note that a di-oxy cyclic phenyl group bearing molecule would be expected to have a different activity from a molecule that does not have this di-oxy cyclic structure as the reactivities between a phenyl bearing two hydroxyl groups and a phenyl bearing di-oxy cyclic structure are expected to be different.

In addition to the above, the function of lignan compounds are conventionally known to be highly sensitive to their structure. Applicants again request the Examiner to consider the two references, Maruyama et al., Biosci. Biotechnol. Biochem 71(3), 677-680 (2007) (Exhibit A), and Akiyama et al., Biosci. Biotechnol. Biochem 71(7), 1745-1751 (2007) (Exhibit B), submitted with the Amendment of October 22, 2010, which demonstrate this point.

Maruyama (Exhibit A) discloses that the antibacterial activity of lignan is closely related to its absolute configuration and functional group (See Abstract). In particular, the conversion of hydroxyl groups (compound 4) to methoxy groups on C-9 and C-9' (compound 3) caused the disappearance of antibacterial activity. Moreover, even two stereoisomers can have different antibacterial activity (See page 679, left column, 2nd paragraph).

Akiyama (Exhibit B) discloses that lignans with similar structures have different antibacterial activity, particularly against *Stapylococcus aureus* (See Tables 1, 2, and 3).

Cited references fail to provide enabling disclosure for using macelignan to treat acne

Third, Neiss '733 fails to provide any demonstration of effectiveness of its generic compounds to treat acne. Neiss '733 fails to provide any evidence that NDGA or macelignan or any other catecholic butane treats acne. Applicants submit that mere one sentence mention three times in Neiss '733 that catecholic butanes may reduce tumor growth and treat acne cannot be

construed to provide an enabling reference to treat acne using macelignan as in the claimed invention.

Deac is cited to provide evidence that NDGA is a bactericidal agent. However, since Deac fails to disclose or suggest the effects of other catecholic butane agents, in particular, macelignan, in killing bacteria and thereby treating acne, the Deac reference fails to remedy the deficiencies of the Neiss '733 reference. Therefore, the presently claimed invention is not obvious over the cited references.

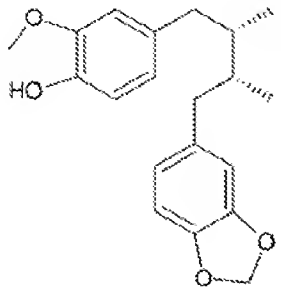
Unexpectedly superior results obtained with the compound of the present invention

The Examiner indicated that Neiss '733 discloses a pharmaceutical composition comprising catecholic butane for the treatment of acne, that Deac discloses nordihydroguaiaretic acid is a preferred compound which has utility in the method of treatment of acne, and that Gibson discloses that *Propionibacterium acnes*, *Staphylococcus epidermis* and *S. aureus* are well-known acne forming bacteria.

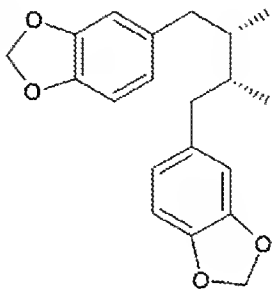
Numerous compounds exist within the genus of catecholic butane. Applicants submit that macelignan has an unexpectedly superior effect on treating acne. The Examiner's attention is directed to the attached Declaration submitted under 37 CFR 1.132 of Dr. Jae-Kwan Hwang, which demonstrates unexpectedly superior minimal inhibitory concentration effects of macelignan versus three structurally similar and well-known compounds, machilin A, *meso*-dihydroguaiaretic acid and nordihydroguaiaretic acid on acne-causing against bacterial (*Propionibacterium acnes*) suspension.

As shown in Table 1 of the Declaration, MICs (minimum inhibitory concentration) of macelignan, machilin A, *meso*-dihydroguaiaretic acid and nordihydroguaiaretic acid on *P. acnes* are 2μg/ml, 500μg/ml, 16μg/ml and 16μg/ml, respectively, indicating that macelignan has unexpectedly superior effect on bacteria caused acne.

The chemical formulas of macelignan, machilin A, *meso*-dihydroguaiaretic acid and nordihydroguaiaretic acid are as below:



< macelignan>



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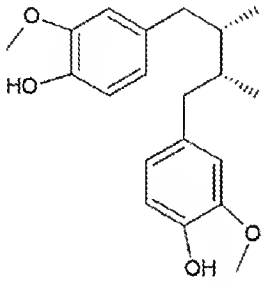
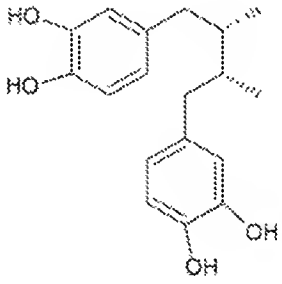


<*meso*-dihydroguaiaretic acid>



<nordihydroguaiaretic acid>

Applicants again assert that the antibacterial activity of lignan is closely related to its absolute configuration and functional group. Accordingly, the present application is not obvious over the cited references.

Conclusion

It is believed that the application is now in condition for allowance. Applicants request the Examiner to issue a notice of Allowance in due course. The Examiner is encouraged to contact the undersigned to further the prosecution of the present invention.

The Commissioner is hereby authorized to charge JHK Law's Deposit Account No. **502486** for such fees required under 37 CFR §§ 1.16 and 1.17 and to credit any overpayment to said Deposit Account No. **502486**.

Respectfully submitted,

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